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**Filed** : May 2, 2002

### **REMARKS**

Applicants have amended the title to more specifically describe the invention. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Applicants have amended Claims 1-8 to remove reference to the Figures. Claims 1-6 and 9-10 have been amended to specify the extracellular domain. Claims 1-5 have been amended to add the limitation that the claimed polypeptides are more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively, or are encoded by a polynucleotide that is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively.

Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. Support for the amendments to Claims 1-6, and 9-10 specifying the extracellular domain can be found in Figure 34, for example. Support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification.

Claims 1-13 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed June 28, 2004. For the reasons set forth below, Applicants respectfully traverse.

### **Correction of Inventorship under 37 CFR §1.48(b)**

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

### **Specification:**

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a

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separate part of the disclosure on a paper copy, a Sequence Listing as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the Sequence Listing, which is also submitted herewith.

**IDS:**

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 11, 2002. Applicants submit herewith more detailed information regarding the publication date of the cited sequences (attached as Exhibit 1).

**Priority Determination:**

The PTO has stated that because the claimed polypeptide has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 2, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/097954 filed 8/26/1998.

Applicants submit that for the reasons stated below, the claimed polypeptides have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 33 and 34 were first disclosed in US Provisional Application 60/097954 filed 8/26/1998 in Figures 1 and 2A-C. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

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**Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness**

The PTO has rejected Claims 1-13 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase “the extracellular domain” as PRO1277 is not disclosed as being expressed on a cell surface. The PTO further objects to the recitation of “the extracellular domain”, “lacking its associated signal sequence” because a signal sequence is not generally considered part of an extracellular domain.

Applicants respectfully submit that the pending claims are not indefinite as both the extracellular domain and the signal peptide regions are well-defined in the specification. For example, Figure 34 indicates that SEQ ID NO: 34 has a transmembrane domain, and thus an extracellular domain, as well as a signal peptide. However, in the interest of advancing prosecution of this application, Applicants will acquiesce to the PTO’s assertion that a signal peptide is not normally considered part of the extracellular domain. By making this concession, Applicants understand that element (c) of Claims 1-6, as well as Claim 9, describes a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 34, **lacking** its associated signal peptide. At the same time, as amended, element (d) of Claims 1-6, as well as Claim 10, describes a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 34, **including** its associated signal peptide. Applicants state that this argument is made only in connection with the instant application, and does not reflect the Applicants’ interpretation of any claims in any related applications.

Applicants have also amended Claims 1-6 and 9-10 to specify the extracellular domain. Thus, Applicants request that the PTO reconsider and withdraw the indefiniteness rejection under 35 U.S.C. § 112, second paragraph.

**Rejection under 35 U.S.C. §101 – Utility**

The PTO has rejected Claims 1-13 as lacking a specific, substantial, and credible utility. The PTO asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1277. One of the asserted utilities for the claimed polypeptides is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1277 cDNA is more highly expressed in normal esophageal tissue and skin compared to esophageal tumor and melanoma tumor, respectively. The PTO has rejected this utility because

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there is no supporting evidence to indicate that the claimed polypeptides encoded by the disclosed polynucleotide of the instant invention are more highly expressed in some normal tissue compared to their tumor counterparts.

The PTO also asserts that the evidence that the polynucleotide is more highly expressed in normal esophageal tissue and skin is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared esophageal and melanoma tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the protein or antibodies for diagnostic or therapeutic purposes. The PTO also states that the specification does not disclose a correlation between any specific disorder and the altered level of the claimed polypeptides, or predict whether the polypeptides would have high or low expression in specific, diseased tissue compared to healthy tissue control. The PTO also argues that because the normal tissue and tumor samples were from different humans, there is no possibility of direct comparison between the two. The PTO also states that because cancerous tissue is aneuploid, the data is unreliable. Finally the PTO argues that there is no necessary correlation between protein expression and nucleic acid levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention

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must be “currently available” to the public in order to satisfy the utility requirement. “Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

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### Substantial Utility

*Applicants have established that the Gene Encoding the PRO1277 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool*

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO1277 polypeptide in normal esophageal tissue and skin compared to esophageal tumor and melanoma tumor, respectively, is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to esophageal tumor and melanoma tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. Applicants also address the PTO's argument that because the normal tissue and tumor samples were from different humans, there is no possibility of direct comparison between the two, and that because cancerous tissue is aneuploid, the data is unreliable. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed polypeptides.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 2). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to

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differentiate tumor from normal.” He explains that, contrary to the PTO’s assertions, “The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.” (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, “If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.”

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, “a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid.” Office Action at 8. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the disclosed nucleic acids, or their corresponding polypeptides, whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding PRO1277 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal esophageal tissue and skin compared to esophageal tumor and melanoma tumor, respectively, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer. As discussed below, this fact leads to utility for the encoded polypeptides.

*Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein*

The PTO argues that there is no supporting evidence that the polypeptide encoded by the nucleotide of the instant invention is more highly expressed in the normal tissue compared to the tumor tissue. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased

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polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that the data pertaining to PRO1277 polynucleotides do not necessarily indicate anything significant regarding the claimed PRO1277 polypeptides.

Applicants submit that those of skill in the art would recognize that amplification of a gene due to aneuploidy will more likely than not lead to an increase in expression of that gene as measured by the level of mRNA. This assertion is supported by numerous references. Orntoft *et al.* (*Molecular and Cellular Proteomics*, 1:37-45 (2002)) (submitted herewith as Exhibit 3) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and teach that “in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts” (Orntoft at 37, column 1, abstract). In addition, Hyman *et al.* (*Cancer Research*, 62:6240-6245 (2002)) (submitted herewith as Exhibit 4) used CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines. They showed that there is “evidence of a prominent global influence of copy number changes on gene expression levels” (Hyman at 6244, column 1, last paragraph).

Additional supportive teachings are also provided by Pollack *et al.* (PNAS, 99:12963-12968 (2002)) (submitted herewith as Exhibit 5) who studied a series of primary human breast tumors and found that “[b]y analyzing mRNA levels in parallel, we have also discovered that *changes in DNA copy number have a large, pervasive, direct effect on global gene expression patterns* in both breast cancer cell lines and tumors.” (Pollack at 12967 at column 1, emphasis added). Their study found that “62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels.” (Pollack at 12963, column 1, abstract). This report is particularly persuasive because the high-resolution comparative genomic hybridization analysis used to assess DNA copy number was particularly sensitive.

Together, these articles collectively teach that in general, gene amplification increases mRNA expression. As discussed below, it is also the established general rule in the art that the



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level of protein expression is directly related to the level of gene expression, so that increased gene expression leads to increased protein expression.

Relying on a single example of one gene, the PTO states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8-9. As an aside, it should be noted that this result may not even be real, as the authors explain: “Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon.” Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO1277 in normal esophageal tissue and skin compared to esophageal tumor and melanoma tumor, respectively. Nothing in Pennica is contrary to Applicants’ assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA. Applicants respectfully submit that by relying on Pennica, the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO’s argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

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Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 6). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 7), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1277 mRNA is expressed at a higher level in normal esophageal tissue compared to esophageal tumor, and normal skin compared to

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melanoma tumor, the PRO1277 polypeptide will also be expressed at a higher level in normal esophageal tissue compared to esophageal tumor, and normal skin compared to melanoma tumor. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed polypeptides as a cancer diagnostic tool.

*The Claimed Polypeptide would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide*

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1277, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 6, Mr. Grimaldi explains that:

However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 8), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 9). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay

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relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

### **Specific Utility**

#### **The Asserted Substantial Utilities are Specific to the Claimed Polypeptides**

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease of condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1277. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1277 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene encoding the PRO1277 polypeptide is more highly expressed in normal esophageal tissue compared to esophageal tumor, and normal skin compared to melanoma tumor. These data are strong evidence that the PRO1277 polypeptide is associated with esophageal tumors and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1277 polypeptide with a specific disease. Use of the claimed polypeptides as a diagnostic tool for cancer, particularly esophageal and melanoma tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

### **Conclusion**

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1277 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene amplification and

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protein expression, the claimed polypeptides cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1277 gene in normal esophageal tissue compared to esophageal tumor, and normal skin compared to melanoma tumor, are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed polypeptides have utility as cancer diagnostic tools. Applicants have also shown that whether the differential expression of the PRO1277 polypeptide is due to aneuploidy or not does not affect its usefulness as a diagnostic tool.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the claimed polypeptide has utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility because there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature associated with PRO1277. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because PRO1277 is differentially expressed in certain cancer tissue compared to the corresponding normal tissue. This is not a general utility that would apply to the broad class of polypeptides.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they

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have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

**Rejection under 35 U.S.C. §112, first paragraph – Enablement**

The PTO rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

**Rejection under 35 U.S.C. §112, first paragraph – Written Description**

The PTO has rejection of Claims 1-5, 12 and 13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polypeptides possess any particular biological activity, particular conserved structure, or other disclosed distinguishing feature, the claims fail the written description requirement. The PTO states that because the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, conception is not achieved until reduction to practice has occurred. Finally, the PTO states that the only factor present in the claim is a partial structure in the form of a recitation of percent identity. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

**The Legal Standard for Written Description**

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure “reasonably conveys to

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artisan that the inventor had possession at that time of the later claimed subject matter.” *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

*The Current Invention is Adequately Described*

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant’s disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns polypeptides having a specified sequence identity with the specified polypeptide sequence of SEQ ID NO: 34, and as amended, with the functional recitation: “wherein said isolated polypeptide is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively.” Based on the detailed description of the cloning and expression of variants of PRO1277 in the specification, the description of the gene expression assay, the actual reduction to practice of sequences SEQ ID NOs: 33 and 34, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims.

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Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

**Rejection under 35 U.S.C. §102(b) – Anticipation**

The PTO rejects Claims 1-10 as anticipated under 35 U.S.C. § 102(b) by Sulston *et al.* (Accession No: Q9UDNO or AAF19243) (hereinafter Sulston), which the PTO states was published December 21, 1999. The PTO states that Sulston discloses an amino acid sequence that has 100% identity to SEQ ID NO: 34 of the instant invention, and therefore anticipates Claims 1-10.

Applicants respectfully traverse.

To be anticipated under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication “more than one year prior to the date of the application for patent in the United States.” 35 U.S.C. § 102(b). Applicants submit that Sulston does not anticipate any of the pending claims because it was not published more than one year prior to the date of the instant application for patent in the United States. The instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/097954 filed 8/26/1998. SEQ ID NOs: 33 and 34 were first disclosed in Figures 1 and 2A-C of US Provisional Application 60/097954 filed August 26, 1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000. According to the PTO, Sulston was published December 21, 1999. Thus, Sulston was not published more than one year prior to the filing of either PCT Application PCT/US00/23328 filed August 24, 2000, or US Provisional Application 60/097954 filed August 26, 1998. The instant application claims priority to both, and therefore Sulston cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b).



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### CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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**DELETION OF INVENTORS**

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.